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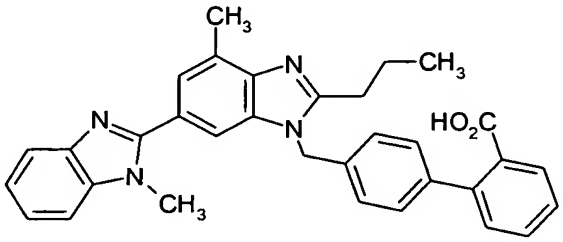
Process for manufacture of telmisartan

Field of the invention

The present invention relates to a new process for preparing 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benzimidazol-1-ylmethyl]biphenyl-2-carboxylic acid (INN: telmisartan).

Background to the invention

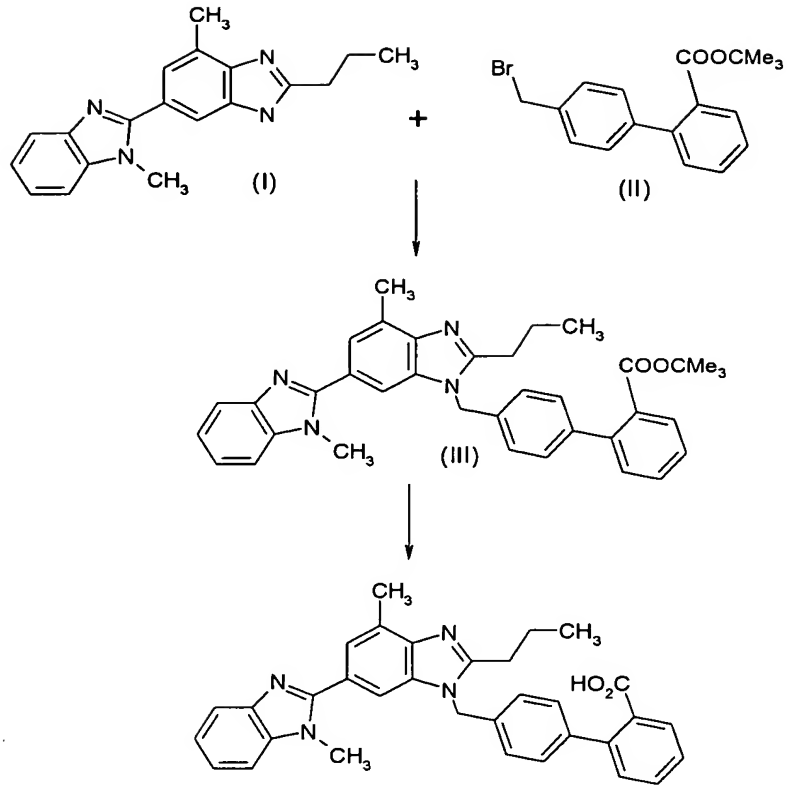
Telmisartan is an angiotensin-II-receptor antagonist which is suitable for the treatment of high blood pressure and other medical indications as described in EP-502314 B1. The active substance has the following structure:



Telmisartan is generally prepared and sold in the form of the free acid. As disclosed in WO 00/43370, crystalline telmisartan occurs in two polymorphic forms which have different melting points. Under the influence of heat and moisture the lower-melting polymorphic form B changes irreversibly into the higher-melting polymorphic form A.

Hitherto, telmisartan has been synthesised industrially by reacting 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole (I) with tert. butyl 4'-bromomethyl-biphenyl-2-carboxylate (II) and subsequently saponifying according to the following Diagram 1.

Diagram 1:



The coupling by nucleophilic substitution in the first reaction step is described in general terms in EP-502314 B1 as process b), while the saponification of the tert. butyl ester group on a laboratory scale using trifluoromethylacetic acid is described in the patent specification as Example 1. Industrially, saponification has up till now been carried out with concentrated aqueous hydrobromic acid. Scaling up the method of synthesis known from the patent specification to a large-scale industrial process was surprisingly beset with problems. Thus, the active substance prepared by the process known up till now can only be obtained in a satisfactory quality after running through a number of process steps (the crude product does not have the required purity until it has been recrystallised twice), while very long centrifuging and drying times are needed when isolating the substance. The telmisartan synthesised on an industrial scale according to Diagram 1 is obtained after working up in the form of a product which has to be subjected to a second crystallisation step to complete the purification. In the said crystallisation step, which is

absolutely essential, the morphology of the end product crystallising out led to unforeseen problems.

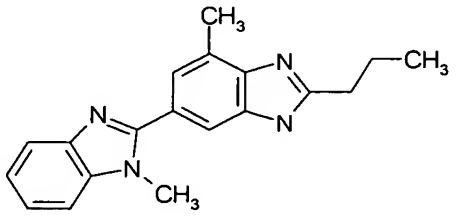
The product precipitated in the form of long needles is difficult to filter, wash and isolate and because of the inclusion of solvent is also characterised by a very long drying time and forms large, very hard lumps during the drying process. Grinding up these lumps results in a dry powder which has a strong tendency to electrostatic charging and is virtually impossible to pour.

The above-mentioned undesirable properties of a product have always proved to be a major obstacle to the large-scale production of a compound as they stop the product being manufactured reproducibly in large quantities and allow a high degree of purity to be achieved only with considerable difficulty or at additional high technical costs.

The aim of the present invention is therefore to provide an alternative method of preparing telmisartan, which can be used on a large scale and allows telmisartan to be easily worked up, purified and isolated without the disadvantages mentioned above.

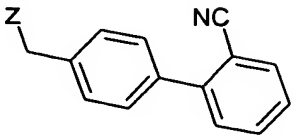
Brief summary of the invention

Surprisingly it has been found that from a technical point of view the reaction of 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole



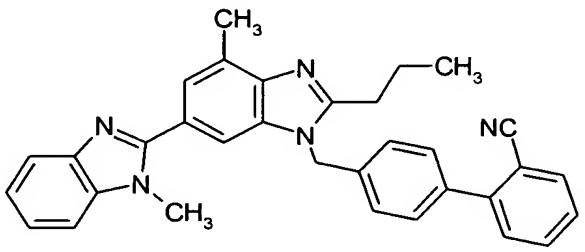
(I)

with a compound of general formula



(IV),

wherein Z denotes a leaving group such as a halogen atom, for example a chlorine, bromine or iodine atom, or a substituted sulphonyloxy group, for example a methanesulphonyloxy, phenylsulphonyloxy or p-toluenesulphonyloxy group, to obtain the compound 2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1"'-methylbenzimidazol-2"'-yl)benzimidazol-1"-ylmethyl]biphenyl



(V)

which may if desired be subjected to working up (Step (a)), and subsequent hydrolysis of the nitrile to the acid function (Step (b)) and if desired conversion of the compound (V) during working up into the hydrochloride, has considerable advantages over the synthesis shown in Diagram 1, and in particular does not have the drawbacks mentioned above for large-scale production by the conventional method.

Detailed description of the invention

Step (a):

The reaction of the compound (I) with a compound of general formula (IV), wherein Z preferably denotes a halogen atom, particularly the bromine atom, is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, diethyl ether, tetrahydrofuran, dioxane,

dimethylsulphoxide, dimethylformamide, dimethylacetamide, dimethylformamide/tert. butanol, dimethylacetamide/tert. butanol, toluene and benzene, optionally in the presence of an acid-binding agent such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium methoxide, potassium methoxide, potassium-tert. pentoxide, potassium tert. butoxide, potassium-n-butoxide, sodium hydride, triethylamine or pyridine, while the latter two may also be used as solvents, for example at a temperature between 0 and 100°C. The base is preferably used in powdered form if it is a solid.

Preferably, the reaction of the compound (I) with a compound of general formula (IV) is carried out in a solvent or mixture of solvents selected from dimethylsulphoxide, dimethylformamide, dimethylacetamide, dimethylformamide/tert. butanol and dimethylacetamide/tert. butanol in the presence of sodium hydroxide, potassium hydroxide or potassium tert. butoxide at a temperature between 0 and 30°C.

Particularly preferably, the reaction of the compound (I) with a compound of general formula (IV) is carried out in dimethylacetamide or dimethylacetamide/tert. butanol in the presence of potassium hydroxide at a temperature between 0 and 20°C.

Working up:
After the reaction has ended the solvent is removed, for example distilled off in a water-jet vacuum, the residue is treated with a solvent in which the nitrile (V) has only limited solubility or is moderately soluble in the heat, for example with an alcohol such as methanol, ethanol, n-propanol, i-propanol, n-butanol or i-butanol, with an aromatic hydrocarbon such as benzene or toluene, with an ethereal solvent such as diethyl ether, tetrahydrofuran, dioxane or tert. butylmethylether, the ethereal solvents and particularly tert. butylmethylether being preferred, or with water, the crystals which may be precipitated after cooling to 10 to 20°C are suction filtered and washed first with the solvent used and then with water. If necessary the product is dried at elevated temperature, for example at 50-100°C, in a vacuum drying cupboard. The

nitrile (V) is generally obtained in excellent yields between 80 and 90 % of theory and with excellent quality (purity according to HPLC > 99.5%).

Step (b):

The subsequent hydrolysis of the nitrile function into a carboxy group is conveniently carried out in water, in an organic solvent or in a mixture of an organic solvent with water, while the organic solvent may be, for example, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, dioxane, ethyleneglycol, propylenglycol, diglyme, dimethylsulphoxide or diethyleneglycol monomethyl ether, in the presence of an acid such as trifluoroacetic acid, trichloroacetic acid, hydrochloric acid, sulphuric acid or phosphoric acid or in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, caesium hydroxide or calcium hydroxide or the anhydrides thereof at temperatures between 80 and 200°C, while the water needed for the reaction may also be a constituent of one of the reagents used, e.g. one of the abovementioned aqueous acids, or may be generated under the reaction conditions from the reagents, possibly from one of the above-mentioned alkali metal hydroxides.

Preferably, the hydrolysis of the nitrile function is carried out in a high-boiling solvent system selected from ethyleneglycol/water and propyleneglycol/water, in the presence of a base, potassium hydroxide being particularly suitable, at temperatures between 140 and 200°C, particularly at a temperature between 155 and 185°C.

Working up:

After the reaction has ended the solvent is removed, for example distilled off in a water-jet vacuum, the residue is diluted with water and taken up in hydrochloric acid, for example with 5 to approx. 32% (conc.) hydrochloric acid, preferably with 5 to 20% hydrochloric acid, whereupon telmisartan hydrochloride crystallises out. The crystal suspension is cooled to 10 to 25°C if necessary and may be stirred at this temperature for a certain length of time, for example up to 3 hours. After the crystals have been suction filtered

they are washed with water and if necessary dried in a vacuum drying cupboard at elevated temperature, for example at 50 to 120°C.

Telmisartan in acid form can be liberated from the telmisartan hydrochloride in the usual way, e.g. by titration with aqueous alkali metal hydroxide solution.

For large-scale production the process according to the invention has the following advantages *inter alia* deserving special mention:

- compounds of formula (IV), particularly 4'-bromomethyl-2-cyanobiphenyl, are mass-produced and may be obtained cheaply;
- the coupling of components (I) and (IV) according to Step (a) may be carried out in a high concentration and at a correspondingly high throughput, while working up particularly using tert. butylmethylether yields the nitrile (V) as a precipitate which is easy to filter and wash, thus dispensing with the need for additional laborious working up procedures;
- the nitrile (V) is obtained in excellent yields of between 80 and 90 % of theory and with excellent quality (purity according to HPLC > 99.5%);
- the saponification of the nitrile (V) in Step (b) also produces excellent yields > 95% of theory;
- the end product telmisartan may be isolated either as an ampholyte or, preferably, by precipitation with hydrochloric acid as a hydrochloride which is easy to filter and hence easy to purify.

The following procedure is used, in a particularly preferred manner according to the invention:

Step (a): All the quantities specified relate to a batch size of 0.1 mol of the compound (I) and if the batch size is altered must be multiplied by a corresponding factor.

50 to 200 ml solvent, preferably 80 to 120 ml, per 0.1 mol of the compound (I) are placed in a suitably dimensioned reaction vessel, the compound (I) is suspended in the solvent and 0.1 to 0.2 mol of base, preferably 0.102 to 0.12

mol, are added batchwise thereto with stirring, while the temperature is maintained at between 10 and 50°C, preferably 15 to 30°C, and when the exothermic reaction has ended stirring may be continued for up to another 3 hours at this temperature. The mixture is cooled to approx. 0 - 10°C, for example approx. 5°C, and then a mixture of 0.1 to 0.2 mol of a compound of general formula (IV), preferably 0.100 to 0.12 mol, with 50 to 200 ml solvent (per 0.1 mol of the compound (IV)) is added dropwise at 10 to 30°C, preferably at approx. 20°C. The reaction mixture is optionally maintained at approx. 0 to 20°C, preferably 5 to 10°C, by cooling with the ice bath. Then it may be rinsed out with a few ml of solvent and stirred for up to another 3 hours at 0 to 20°C.

In another embodiment the base is placed in 30 to 100 ml solvent, preferably dimethylformamide, dimethylacetamide, dimethylformamide/tert. butanol or dimethylacetamide/tert. butanol, at 10 to 30°C, stirred for up to an hour at about 20°C, for example, and then a suspension of the compound (I) in 30 to 100 ml solvent is slowly metered in at this temperature. All the other steps are the same as in the previous embodiment. The solvent mixtures specified are used in a ratio by volume of amide : tert. butanol = 10 : 1 to 2.5 : 1, for example 5 : 1.

Working up:
The solvent is conveniently largely distilled off under reduced pressure, for example under a water-jet vacuum, whereupon the product crystallises out. After the residue has cooled to approx. 40 to 80°C, preferably about 60°C, it is diluted with 100 to 300 ml solvent (per 0.1 mol batch size, based on compound (I)), preferably tert. butylmethylether, and stirred for up to 5 hours without any input of energy. The mixture is cooled to 0 to 30°C, preferably 15 to 20°C, and stirred for up to a further 5 hours at this temperature. The crystals are suction filtered and washed batchwise with 50 to 150 ml of the solvent and then with 200 to 300 ml of water. The product is dried in the vacuum drying cupboard at 50 to 100°C, preferably about 60°C.

Step (b): Unless otherwise stated, all the amounts specified are based on a batch size of 0.05 mol of the compound (V) and must be multiplied by a corresponding factor if the batch size is altered.

0.05 mol of the compound (V), 200 to 300 ml of the organic solvent, 0.5 to 5 ml of water and 0.3 to 0.5 mol of the base are combined and heated to the boiling temperature of the solvent system used, i.e. if the preferred ethyleneglycol/water mixture is used, it is heated to 140 to 200 °C, preferably to 155 to 185°C. The mixture is stirred for up to 24 hours at this temperature.

In another embodiment 0.361 mol of the nitrile (V) are placed in 1.5 to 2 L of the organic solvent, preferably ethyleneglycol, 25 to 50 ml of water and 2.5 to 3 mol of the base are added and the mixture is heated to 140 to 200 °C, preferably to 155 to 185°C, for up to 24 hours, with stirring. All the other steps correspond to those in the previous embodiment.

Working up:
The amounts given are based on a batch size of 0.05 mol of compound (V). The solvent is conveniently eliminated under reduced pressure, for example distilled off under a water jet vacuum, the residue is diluted with 30 to 100 ml of water, preferably about 5 ml, and stirred into a mixture of 100 to 150 ml of water (preferably about 125 ml) and 40 to 60 ml (preferably about 50 ml) conc. hydrochloric acid (approx. 32%), possibly rinsing with water. The telmisartan hydrochloride that crystallises out is cooled to 10 to 25°C and is stirred for up to 3 hours at this temperature. After the crystals have been suction filtered they are washed with 50 to 200 ml of water and dried at 50 to 120°C in a vacuum drying cupboard.

The Examples that follow serve to illustrate the invention and relate to exemplifying embodiments of the methods of synthesis according to the invention for preparing telmisartan, but without restricting the invention to their contents.

Example 1

2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1'"-methylbenzimidazol-2"'-yl)benzimidazol-1"-ylmethyl]biphenyl

32.24 g of 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole x H_2O are placed in 100 ml of dimethylacetamide (DMA), 11.8 g of potassium tert. butoxide are added batchwise with stirring at approx. 20°C and then the mixture is stirred for one hour at about 20°C. The mixture is cooled to 5°C and then a mixture of 28.6 g of 4-bromomethyl-2'-cyano-biphenyl and 95 ml of DMA (dissolved at approx. 20°C) is added dropwise over about 30 minutes. The temperature of the reaction mixture is maintained at approx. 5 – 10°C by cooling with the ice bath. Then it is rinsed with 5 ml of DMA and stirred for a further 1.5 hours at 5 – 10°C.

The solvent is largely distilled off under a water jet vacuum, during which time the product crystallises out. The residue is cooled to 60°C, diluted with 230 ml of tert. butylmethylether and stirred for 1 hour without any energy input, then cooled to 15 – 20°C and stirred for another hour at this temperature. The crystals are suction filtered, washed batchwise with 100 ml of tert. butylmethylether, then with 250 ml of water and then dried in a vacuum drying cupboard at 80°C.
Yield: 43.3 g (87.5% of theory).
Melting point:196 – 197°C
HPLC: > 99.9 %

Example 2

2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1'"-methylbenzimidazol-2"'-yl)benzimidazol-1"-ylmethyl]biphenyl

32.24 g of 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole x H_2O are placed in 100 ml of DMA, 6.9 g of potassium hydroxide (powder) are added batchwise with stirring at approx. 20°C and then stirred for one hour at about 20 to 25°C. The mixture is cooled to 5°C and then 28.6 g of 4-bromomethyl-2'-cyano-biphenyl in 95 ml of DMA (dissolved at approx. 20°C)

are added dropwise over approx. 30 minutes. The temperature of the reaction mixture is maintained at approx. 5 – 10°C by cooling with the ice bath. Then it is rinsed with 5 ml of DMA and stirred for a further 1.5 hours at 5 – 10°C.

The solvent is largely distilled off under a water jet vacuum, during which time the product crystallises out. The residue is cooled to 60°C, diluted with 225 ml of tert. butylmethylether and stirred for 1 hour without any energy input, then cooled to 15 – 20°C and stirred for another hour at this temperature. The crystals are suction filtered, washed batchwise with 100 ml of tert. butylmethylether, then with 250 ml of water and then dried in a vacuum drying cupboard at 80°C.
Yield: 40.45 g (81.7% of theory).
Melting point:196 – 197°C
HPLC: > 99.9 %

Example 3

2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1'"-methylbenzimidazol-2'"-yl)benzimidazol-1"-ylmethyl]biphenyl

6.9 g of potassium hydroxide (powder) are placed in 50 ml of DMA, stirred for 15 minutes at 20 to 25°C and then a suspension of 32.24 of 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole x H_2O in 50 ml of DMA is metered in at 20 to 25°C. After it has all been added the vessels are rinsed with 10 ml of DMA and then stirred for another hour at 20 to 25°C. The mixture is cooled to 5°C and then 28.6 g 4-bromomethyl-2'-cyano-biphenyl in 95 ml of DMA (dissolved at approx. 20°C) are metered in. The temperature of the reaction mixture is maintained at approx. 5 – 10°C by cooling with the ice bath. Then it is rinsed with 5 ml of DMA and stirred for a further hour at 5 – 10°C.

The solvent is largely distilled off under a water jet vacuum, during which time the product crystallises out. The residue is cooled to 60°C, diluted with 250 ml of tert. butylmethylether and stirred for 2 hours without any input of energy. The crystals are suction filtered, washed batchwise with 100 ml of tert.

butylmethylether, then with 250 ml of water and then dried in a vacuum drying cupboard at 80°C.
Yield: 43.37 g (87.5% of theory).
Melting point:196 – 198°C
HPLC: 99.1 %

Example 4

2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1'"-methylbenzimidazol-2'"-yl)benzimidazol-1"-ylmethyl]biphenyl

53.4 g of potassium hydroxide (powder) are placed in 385 ml of DMA and then a suspension of 248.25 g of 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole x H_2O in 385 ml of DMA are metered in at 20 to 25°C. After it has all been added the vessels are rinsed with 77 ml of DMA and then stirred for another hour at 20 to 25°C. The mixture is cooled to 5°C and then 209.5 g of 4-bromomethyl-2'-cyano-biphenyl in 731.5 ml of DMA (dissolved at approx. 20°C) are metered in. The temperature of the reaction mixture is maintained at approx. 5 – 10°C by cooling with the ice bath. Then it is rinsed with 38.5 ml of DMA and stirred for a further hour at 5 – 10°C.

The solvent is largely distilled off under a water jet vacuum, during which time the product crystallises out. The residue is cooled to 60°C, diluted with 1925 ml tert. butylmethylether and stirred for 2 hours without any energy input. The crystals are suction filtered, washed batchwise with 770 ml of tert. butylmethylether/DMA = 9:1, then with 1925 ml of water and twice with 250 ml of tert. butylmethylether and then dried at 80°C in a vacuum drying cupboard.
Yield: 322.15 g (84.4% of theory).
Melting point:197 – 198.5°C
HPLC: 99.6%

Example 5: Telmisartan x HCl

25 g of 2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1"'-methylbenzimidazol-2"'-yl)benzimidazol-1"-ylmethyl]biphenyl, 250 ml of ethyleneglycol, 0.9 ml of water and 24.75 g of caustic potash (>85%) are combined and heated to 160°C with stirring. The mixture is stirred for 13.5 hours at this temperature.

The solvent is largely distilled off under a water jet vacuum, the residue is cooled to 100°C, diluted with 50 ml of water and stirred into a mixture of 125 ml of water and 50 ml of conc. hydrochloric acid (approx. 32%), rinsing with 50 ml of water. The telmisartan hydrochloride that crystallises out is cooled to 15 to 20°C and stirred for approx. 1 hour at this temperature. After the crystals have been suction filtered they are washed with 100 ml of water and dried in a vacuum drying cupboard at 100°C.
Yield: 27.3 g (98.2% of theory).
HPLC: 99.9%.

Example 6: Telmisartan x HCl

179 g of 2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1"'-methylbenzimidazol-2"'-yl)benzimidazol-1"-ylmethyl]biphenyl are placed in 1611 ml of ethyleneglycol, 32.5 ml of water and 178.7 g of potassium hydroxide (powder) are added and the mixture is heated to 150 to 160°C with stirring. The mixture is stirred for approx. 15 hours at this temperature and then cooled to 100°C.

The solvent is largely distilled off under a water jet vacuum, the residue is cooled to 100°C, diluted with 358 ml of water and stirred into a mixture of 716 ml of water and 358 ml of conc. hydrochloric acid (approx. 32%), rinsing with 179 ml of water. The telmisartan hydrochloride that crystallises out is stirred for one hour at 60°C, cooled to 15 to 20°C and stirred for approx. 1 more hour at this temperature. After the crystals have been suction filtered they are washed with 716 ml of water and dried in a vacuum drying cupboard at 100°C.
Yield: 192.1 g (96.5% of theory).
HPLC: >99.9%

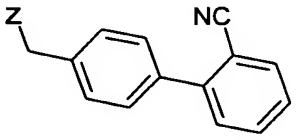
Example 7: Telmisartan

5.51 g of telmisartan x HCl are dissolved in 50 ml of 40% acetic acid while refluxing. Then the brown solution is filtered hot through 1.1 g of charcoal, washed with 2.5 ml of 40% acetic acid and 2.5 ml of 4N NaOH are added dropwise to the light brown filtrate with stirring at 80 – 90°C. The telmisartan crystallises out, the suspension is diluted with 30 ml of water and slowly cooled to ambient temperature. The telmisartan is suction filtered and washed with 50 ml of water. The telmisartan is dried at 80°C in a vacuum drying cupboard.

Yield: 4.80 g (93.3% of theory)

Abstract

The present invention relates to a new process for preparing telmisartan by reacting 2-n-propyl-4-methyl-6-(1'-methylbenzimidazol-2'-yl)-benzimidazole with a compound of general formula



(IV),

wherein Z denotes a leaving group, to obtain the compound 2-cyano-4'-[2"-n-propyl-4"-methyl-6"-(1"'-methylbenzimidazol-2"'-yl)benzimidazol-1"-ylmethyl]biphenyl, and subsequently hydrolysing the nitrile function to obtain the acid function.